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### **REMARKS**

Claims 1 – 10, 43 – 45 and 49 are pending in the application. Claims 4 – 42 and 46 – 48 have been cancelled. Claims 1 and 49 have been amended. No new claims have been added.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

#### **Claim Rejections Withdrawn**

The Examiner has withdrawn the rejection of claims 1 – 3, 8 and 43 – 45 under 35 USC 102(b) as being anticipated by US Patent 5,608,060.

The Examiner has withdrawn the rejection of claims 1 – 3, 8 – 10, 43 – 45 and 49 under 35 USC 102(e) as being anticipated by US Patent 7,265,085.

The Examiner has withdrawn the rejection of claims 1 – 3, 8 – 10, 43 – 45 and 49 under 35 USC 102(e) as being anticipated by US Patent 7,265,085.

The Examiner has withdrawn the rejection of claims 1 and 8 – 12 under 35 USC 103 (a) over US Patent 7,265,085.

#### **35 U.S.C. §112, first paragraph**

##### **Enablement**

Claims 1 – 3, 8 – 10 and 43 – 45 were rejected under 35 U.S.C. §112, first paragraph. The Examiner argues that “the specification, while being enabling only for a method of making a

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targeted glycoconjugate comprising a specific bioactive agent and a specific targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP-galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase for detection assays, does not reasonably provide enablement for any targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound for use in any medical therapy, any pharmaceutical composition comprising any targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and then targeting compound are joined by any modified saccharide compound.” (Office Action, p.3). Applicants respectfully disagree.

The instant claims are directed to a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.

The Examiner argues that “(e)nablement is not commensurate in scope with how to make any targeted glycoconjugate comprising any bioactive agent and any targeting compound, any targeting compound is any glycoprotein wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound wherein said modified saccharide compound comprises galactose and any reactive functional group, any functional group such as ketone group attached to the C2 position of the galactose ring for any and all medical therapy or diagnosis.” (Office Action, p.4).

The claims have been amended to recite that **the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), where the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.** Accordingly, the specification enables any person skilled in the art to make and use the invention commensurate in scope of the present claims.

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The Examiner argues that the claims encompass innumerable targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound. (Office Action, p.4).

Applicants point out that the specification teaches saccharide compounds of the present invention, and in particular galactose, are particularly modified at the C2 position. The specification teaches that the C2 position is favorable over other positions on the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C2 positions. Applicants teach that appending the ketone functionality at the C-2 position of the galactose ring. At page 48 of the specification, Applicants describe a strategy for the rapid and sensitive detection of O-GlcNAc glycosylated proteins, where experiments show that "the ketone functionality was appended at the C-2 position of the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C-2 positions, including 2-deoxy, 2-amino, and 2-N-acetyl substituents (Ivan et al., 2001; Wong et al., 1995) (and)... 2-deoxy-Gal was transferred at rates comparable to Gal, whereas 3-, 4, and 6-deoxy-Gal were transferred at reduced rates." (page 48).

Accordingly, the claims recite that the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. Further, the specification teaches modification of the saccharide to include a functional group, such as a ketone group, aids in the attachment of the bioactive agent, and provides examples of such attachments. For example, on page 10, the specification teaches that "the modified saccharide (S) may include a ketone moiety which can be reacted with an amino group of a bioactive agent of interest so as to form a covalent bond between the two."

The specification teaches at page 11 beginning at line 5, various methods that can be used to bind the bioactive agent to the modified saccharide:

The methods used to bind the bioactive agent (B) to the modified saccharide (S) depend on the structure of the bioactive agent. The bioactive compounds may preferably include a functional group which may be useful, for example, in forming covalent bonds with the saccharide residue, which are not generally critical for the activity of the bioactive agent. Examples of such functional groups

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include, for example, amino ( $-\text{NH}_2$ ), hydroxy ( $-\text{OH}$ ), carboxyl ( $-\text{COOH}$ ), thiol ( $-\text{SH}$ ), phosphate, phosphinate, ketone group, sulfate and sulfinate groups. If the bioactive compounds do not contain a useful group, one can be added to the bioactive compound by, for example, chemical synthetic means. Where necessary and/or desired, certain moieties on the components may be protected using blocking groups, as is known in the art, see, e.g., Green & Wuts, *Protective Groups in Organic Synthesis* (John Wiley & Sons) (1991).

Exemplary covalent bonds by which the bioactive compounds may be associated with the saccharide residue (S) include, for example, amide ( $-\text{CONH}-$ ); thioamide ( $-\text{CSNH}-$ ); ether ( $\text{ROR}'$ , where R and R' may be the same or different and are other than hydrogen); ester ( $-\text{COO}-$ ); thioester ( $-\text{COS}-$ );  $-\text{O}-$ ;  $-\text{S}-$ ;  $-\text{S}_{\text{sub } n}-$ , where n is greater than 1, preferably about 2 to about 8; carbamates;  $-\text{NH}-$ ;  $-\text{NR}-$ , where R is alkyl, for example, alkyl of from about 1 to about 4 carbons; urethane; and substituted imidate; and combinations of two or more of these.

Covalent bonds between a bioactive agent (B) and a modified saccharide residue (S) may be achieved through the use of molecules that may act, for example, as spacers to increase the conformational and topographical flexibility of the compound. Examples of such spacers include, for example, succinic acid, 1,6-hexanedioic acid, 1,8-octanedioic acid, and the like, as well as modified amino acids, such as, for example, 6-aminohexanoic acid, 4-aminobutanoic acid, and the like.

The Examiner argues that "(t)he specification provided little or no guidance as to the binding specificity of the targeting compound beyond the mere mention of a laundry list of targeting molecules, bioactive agents joined by a list of modified saccharide compounds." (Office Action, p.4). The Examiner argues that "there is no guidance as to the binding specificity of the targeting compound for the claimed glycoconjugated (and) given the numerous unspecified glycoconjugates, there is a lack of in vivo working example of such glycoconjugate could treat any disease such as AIDS." (Office Action, p.4).

According to the MPEP at 2164.02, "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." Moreover,

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Applicant does not need to demonstrate therapeutic effects for particular diseases to enable the invention as claimed.

The invention as claimed is a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.

The present invention features glycoconjugates in which a bioactive agent is bound through a modified saccharide residue, e.g., UDP-GalNAc, to a compound which has an affinity for a target cell.

In the Examples, Applicants describe the rapid and sensitive detection of O-GlcNAc glycosylated proteins. As described by Applicants at page 48 of the specification, "the approach capitalizes on the substrate tolerance of GalT, which allows for chemoselective installation of an unnatural ketone functionality to O-GlcNAc modified proteins. The ketone moiety has been well-characterized in cellular systems as a neutral, yet versatile, chemical handle (Cornish et al., 1996; Mahal et al., 1997; Datta et al., 2002). Here, it serves as a unique marker to "tag" O-GlcNAc glycosylated proteins with biotin. Once biotinylated, the glycoconjugates can be readily detected by chemiluminescence using streptavidin conjugated to horseradish peroxidase (HRP)." (line 14 – 21).

Applicants demonstrate in the Examples the ability of GalT to label the peptide TAPTS(O-GlcNAc)TIAPG, which encompasses an O-GlcNAc modification site within the protein CREB. Applicants use wild-type GalT and show that only partial transfer of the keto-sugar was observed by LC-MS, however when the Y289L mutant was used there was greater activity and complete conversion. (see page 40, line 14 – 22). Further, Applicants show that the same strategy can be used for the labeling of the O-GlcNAc glycosylated protein CREB (see, e.g. page 45, line 8 – 23).

As described in the specification at page 10, line 15, "the targeting compound (T)...is covalently bonded to a saccharide residue (S) with the use of a galactosyltransferase enzyme, preferably beta-1,4-galactosyltransferase (GalT). In one embodiment of the invention, a modified saccharide (S) is covalently associated with the targeting compound with the use of a genetically engineered GalT, such as Y289L GalT (as discussed above). **The targeting compound can be any**

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**naturally occurring glycoprotein, glycolipid or carbohydrate or can be engineered, through chemical or recombinant techniques.** For example, if the targeting compound does not include a GlcNAc residue, the compound can be engineered, either through recombinant or chemical techniques known in the art, so as to include such a residue. Preferably, the targeting compound includes an N-acetylglucosamine (GlcNAc) residue.”

The specification teaches a wide variety of bioactive agents that may be used, and that are known in the art as useful in therapeutic or diagnostic methods or in medical therapies. For example beginning at page 12, line 8, the specification teaches:

A wide variety of bioactive agents (B) may be included in the compounds of the present invention, such as any biologically active, therapeutic or diagnostic compound/composition. In general, the term bioactive agent includes, but is not limited to: polypeptides, including proteins and peptides (e.g., insulin); releasing factors and releasing factor inhibitors, including Luteinizing Hormone Releasing Hormone (LHRH) and gonadotropin releasing hormone (GnRH) inhibitors; carbohydrates (e.g., heparin); nucleic acids; vaccines; and pharmacologically active agents such as anti-infectives such as antibiotics and antiviral agents; anti-fungal agents; analgesics and analgesic combinations; anesthetics; anorexics; anti-helminthics; anti-arthritis agents; respiratory drugs, including anti-asthmatic agents and drugs for preventing reactive airway disease; anticonvulsants; antidepressants; anti-diabetic agents; anti-diarrheals; anticonvulsants; antihistamines; anti-inflammatory agents; toxins, anti-migraine preparations; anti-nauseants; anticancer agents, including anti-neoplastic drugs; anti-parkinsonism drugs; anti-pruritics; anti-psychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including potassium and calcium channel blockers, beta-blockers, alpha-blockers, cardioprotective agents; anti-arrhythmics; anti-hyperlipidemic agents; anti-hypertensives; diuretics; anti-diuretics; receptor agonists, antagonists, and/or mixed function agonist/antagonists; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; vasoconstrictors; cough and cold preparations, including decongestants; enzyme inhibitors; hormones such as estradiol, testosterone, progesterone and other

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steroids and derivatives and analogs, including corticosteroids; hypnotics; hormonolytics; immunosuppressive agents; muscle relaxants; parasympatholytics; central nervous system stimulants; diuretics; hypnotics; leukotriene inhibitors; mitotic inhibitors; muscle relaxants; genetic material, including nucleic acid, RNA, DNA, recombinant RNA, recombinant DNA, antisense RNA, antisense DNA, hammerhead RNA, a ribozyme, a hammerhead ribozyme, an antigenic nucleic acid, a ribo-oligonucleotide, a deoxyribonucleotide, an antisense ribo-oligonucleotide, and/or an antisense deoxyribo-oligonucleotide; psychostimulants; sedatives; anabolic agents; vitamins; herbal remedies; anti-metabolic agents; anxiolytics; attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) drugs; neuroleptics; and tranquilizers.

Beginning at page 24, the specification discusses therapeutic uses. Accordingly, demonstration of specific therapeutic effects for particular diseases to enable the invention as claimed is not necessary.

Applicants have further exemplified that antibodies can be galactosylated with Y289L GalT having a chemical handle at the C2 position in Bioconjugate Chem. 2009, 20, 1228 – 1236 (provided herein). Applicants describe the utility of Y289L GalT to transfer a sugar residue with C2-keto-Gal (or GalNAz) from their UDP derivatives to the N-acetylglucosamine residue of glycoproteins or glycopeptides. (see, e.g. Figure 5 on page 1233). Moreover, Applicants teach that the conjugation technology is a viable method that can be used for detection and targeting therapies. (see, p.1229). In Bioconjugate Chem. 1009, 20, 1383- 1389 (provided herein). Applicants describe the biological activity of the described glycoconjugates. For example, Applicants describe C-terminal extended fusion polypeptides of recombinant scFv fusion proteins that are used as the acceptor substrate for human polypeptide-alpha-N-acetylgalactosaminyltransferase II that transfers either GalNAc or 2-keto-Gal from their respective UDP-sugars to the side-chain hydroxyl group of the Thr residue(s). The fusion scFv proteins with the modified galactose are then conjugated with a fluorescence probe, Alexa488, that carries an orthogonal reactive group. The fluorescence labeled scFv proteins bind specifically to a human breast cancer cell line (SK-BR-3) that overexpresses the HER2 receptor, indicating that the in vitro folded scFv fusion proteins are biologically active and the presence of

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conjugated multiple Alexa488 probes in their C-terminal end does not interfere with their binding to the antigen.

Taken together, the teachings of the specification and knowledge of one of skill in the art enables one of skill in the art to practice the full scope of the claimed invention without having to resort to undue experimentation. Applicants accordingly request that the rejection be reconsidered and withdrawn.

### Written Description

Claims 1 – 3, 8 – 12 and 43 – 45 were rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. (Office Action, p.8). Applicants respectfully disagree.

The Examiner argues that “claims 1, 9 and 45 are broadly drawn to any targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound for use in any medical therapy.” (Office Action, p.8). Applicants respectfully disagree.

The Examiner argues that “claim 2 is broadly drawn to any targeted glycoconjugate comprising any bioactive agent such as any and all polypeptide, any and all releasing factor, any and all releasing factor inhibitor, any and all carbohydrate, any and all nucleic acid and any and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound wherein the modified saccharide compound comprises galactose and any reactive functional group attached to the C2 position of the galactose ring for use in any medical therapy.” (Office Action, p.8). Applicants respectfully disagree.

The Examiner argues that “claim 3 is broadly drawn to any targeted glycoconjugate comprising any bioactive agent and any targeting compound such as any glycoprotein wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound.” (Office Action, p.8 - 9). Applicants respectfully disagree.

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The Examiner argues that "claim 8 is broadly drawn to any targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound such as modified galactose." (Office Action, p.0). Applicants respectfully disagree. Claim 8 has been cancelled. Applicants respectfully request that this rejection be withdrawn.

The Examiner argues that "claim 10 is broadly drawn to any targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified galactose further comprises any reactive functional group." (Office Action, p.9). Applicants respectfully disagree. Claim 10 has been cancelled. Applicants respectfully request that this rejection be withdrawn.

The Examiner argues that "claim 43 is broadly drawn to any and all pharmaceutical composition comprising any and all targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound and a pharmaceutically acceptable carrier." (Office Action, p.9). Applicants respectfully disagree.

The Examiner argues that "claim 44 is broadly drawn to a kit comprising any targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound and a pharmaceutically acceptable carrier." (Office Action, p.9). Applicants respectfully disagree.

In the interest of compact prosecution, the above rejections will be addressed together.

The Examiner argues that "the scope of each genus includes many members with widely differing structural, chemical, and physiochemical properties of targeting compound and bioactive agent such as widely differing amino acid sequences, nucleotide sequences and biological functions in the claimed glycoconjugate." (Office Action, p.10). The Examiner argues further that "each genus is highly variable because a significant number of structural and biological differences between genus members exist." (Office Action, p.10). Applicants disagree.

As amended, the claims are sufficiently described in the specification.

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The claims have been amended to particularly recite targeted glycoconjugate compounds comprising a bioactive agent and a targeting compound, wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.

As discussed above, the claims have been amended to recite that **the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), where the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.**

The specification teaches that saccharide compounds of the present invention, and in particular galactose, are particularly modified at the C2 position. The specification teaches that the C2 position is favorable over other positions on the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C2 positions. Applicants describe a strategy for the rapid and sensitive detection of O-GlcNAc glycosylated proteins, where experiments show that "the ketone functionality was appended at the C-2 position of the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C-2 positions, including 2-deoxy, 2-amino, and 2-N-acetyl substituents (Ilan et al., 2001; Wong et al., 1995) (and)... 2-deoxy-Gal was transferred at rates comparable to Gal, whereas 3-, 4, and 6-deoxy-Gal were transferred at reduced rates." (page 48).

Modified saccharide compounds are described at page 9.

Targeting compounds are described at page 10 and page 18. For example, antibodies are given as an example of a targeting compound at page 20.

Bioactive agents are described beginning at page 10.

Applicants submit that the claims are sufficiently described in the specification to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully request that the foregoing rejections be withdrawn.

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35 U.S.C. §103(a)

Claims 1 – 3, 8 – 10, 43 – 45 and 49 stand rejected under 35 U.S.C. §103(a) over US Patent No. 7,265,085 (the '085 reference herein) and in view of Ramakrishnan et al. (J Biol Chem 277 (23):20833 – 20839, June 2002) and Hang et al. (J Am Chem 123: 1242 – 1243, 2001). Applicants respectfully traverse the rejection.

The claims have been set forth above.

The Examiner argues that "(t)he '085 reference teaches various targeted glycoprotein such as transferring-SA linker-GDNF wherein the reference targeting compound such as transferrin and bioactive agent such as GDNF are joined by a modified saccharide compound such as  $\alpha$ -Glc-NAc modified galactose using beta-1,4 galactosyl transferase." (Office Action, p.14). The Examiner argues that

The '085 reference is directed to methods of remodeling a peptide to attach a specific glycan structure. The '085 reference teaches that at least one of the glycosyl donors comprises a modifying group (and) preferably, the modifying group is a member selected from the group consisting of a polymer, a therapeutic moiety, a detectable label, a reactive linker group, a targeting moiety and a peptide. That is, the '085 reference teaches that the glycans structures are remodeled in order to be useful (see col. 63 – 65). Conjugates of the invention are described beginning at col. 66:

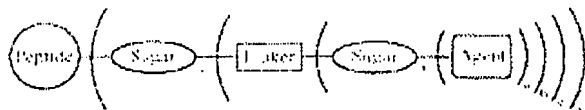
In a first aspect, the present invention provides a conjugate between a peptide and a selected moiety. **The link between the peptide and the selected moiety includes an intact glycosyl linking group interposed between the peptide and the selected moiety.** As discussed herein, the selected moiety is essentially any species that can be attached to a saccharide unit, resulting in a "modified sugar" that is recognized by an appropriate transferase enzyme, which appends the modified sugar onto the peptide. (col. 66 – 67, emphasis added).

Typical conjugates of the invention are shown by the structure at col. 67, line 5, where "symbols a, b, c, d and s represent a positive, non-zero integer; and t is either 0 or a positive integer. The 'agent' is a therapeutic agent, a bioactive agent, a detectable label, water-soluble

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moiety or the like... (and) (t)he linker can be any of a wide array of linking groups, infra... (or) a single bond or a "zero order linker."



The '085 reference exemplifies such a conjugate at col. 68, line 6, where "EPO is conjugated to transferrin... (or) EPO is conjugated to glial derived neurotrophic growth factor (GDNF). In these embodiments, each conjugation is accomplished via a **bifunctional linker that includes an intact glycosyl linking group at each terminus of the PEG moiety**, as aforementioned." (emphasis added).

Clearly, the glycoconjugates that are taught by the '085 reference are different from the present claims, where the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), where the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. The structure of these conjugates is different from the present invention as claimed.

None of the Ramakrishnan or Hang references cure the defects of the '085 reference.

The Examiner argues that "Ramakrishnan et al. teach a modified beta-1,4 galactosyltransferase having a tyrosine at position 289 substitute for Lysine that enhances the GalNAc-transferase activity equal to that of Gal-T activity." (Office Action, p.15).

The Examiner argues that "Hang et al. teach the use of unnatural or modified monosaccharide such as 2-ketosugars or 2-keto isotere of GalNAc sugar or 2-acetaminodugars as the substrate for GalNAc transferase for metabolic glycoprotein engineering in CHO cells. Hang et al. further teach the ketone reactive group produced by 2-ketosugars can be used as a molecular handle and more accessible for chemical reaction with biotin hydrazide." (Office Action, p.15).

The Ramakrishnan and Hang references do not make up for the defects of the '085 reference. The '085 reference does not teach a targeted glycoconjugate comprising a bioactive agent and targeting compound that are joined by a modified UDP galactose acetyl group (UDP-GalNAc). Nor

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does the '085 reference provide teaching or suggestion to modify any position of the saccharide ring preferably over any other position. It would not have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the beta-1,4 galactosyl transferase that catalyse the transfer of galactose in the target conjugate of the '085 patent for the modified beta-1,4 galactosyltransferase taught by the Ramakrishnan reference using any modified monosaccharide such as 2-ketosugars or 2-ketoisostere of GalNAc as a molecular handle as taught by the Hang reference.

In view thereof, reconsideration and withdrawal of the rejection are requested.

### CONCLUSION

For the reasons provided, Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner.

If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

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Respectfully submitted,



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